REMARKS

Claims 2-8, 28-35 and 39-41 presently appear in this case. No claims have been allowed. The official action of July 29, 2004, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for treating tumors in mammals or for inhibiting tumor cell proliferation in mammals by administering to a mammal in need thereof an effective amount of leptin or a mutein, fragment, or fusion protein thereof, or a salt or functional derivative thereof.

Claims 2-8, 28-35 and 37-39 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that claims 28 and 31 recite "stringent conditions that include washing conditions" 12-20 degrees "below the calculated Tm of the hybrid under study." The examiner states that the metes and bounds of the stringent conditions cannot be determined because the "hybrid under study" is itself not limited by the claim language. The examiner states that in order to determine what the hybrid under study consists of, it would be necessary to know the constitution of the nucleic acid which was being hybridized to the nucleic acid encoding leptin. This rejection is respectfully traversed.

Those of ordinary skill in the art would understand that the hybrid under study would be a hybrid of the probe (the DNA of leptin) and a perfectly complimentary target DNA. This would be the temperature at which one would expect to bind only leptin. As long as one is looking for muteins, the washing conditions are set so as to be below that calculated Tm. Thus, washing conditions at 12-20° below that calculated Tm will allow hybridization with target DNA that is not perfectly complementary. Those of ordinary skill in the art would understand that one does not set the conditions 12-20° below the calculated Tm of the probe with a mutein. That would make no sense. The Tm of leptin with its perfectly complementary target DNA is readily calculable. The claims under rejection are not indefinite. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 1-8, 28, 30, 31, 32, 34 and 37-39 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the administration of leptin or fragments of leptin, does not reasonably provide enablement for the administration of leptin muteins, or fragments of leptin muteins, or fusion proteins of leptin muteins. The examiner states that without further teachings in the specification, one of skill in the art would not be assured that a leptin mutein can be made having as little as

60, 70 or 80% sequence identity with leptin, with the ability to inhibit IGF-I induced or insulin induced proliferation of T-47D cells or MCF7 cells. The examiner states that even a single amino acid substitution can dramatically affect the biological activity and characteristic of a protein, and therefore it could not be predicted that a variant protein that shares as little as 60, 70 or 80% sequence identity with leptin would function as suggested. The examiner states that it would take undue experimentation in order to find muteins and variants that function as leptin. This rejection is respectfully traversed.

The examiner has objected to the definition of muteins with as little as 60, 70 or 80% sequence identity to leptin. Accordingly, claim 28 has now been amended to specify that the mutein must have at least 90% sequence identity, and claims 37 and 38 have been deleted. In view of the very substantial degree of identity that is necessary, it would not take undue experimentation to test any such muteins using the assay specified in the claims. It is not necessary to know, or to be able to predict in advance, which variations in the amino acid sequence of leptin would maintain the ability of leptin to inhibit the IGF-I-induced or insulin-induced proliferation of the human breast cancer cell line T-47D or MCF7. It is not necessary to decide whether protein chemistry

is predictable or unpredictable. The point is that mutations in the DNA-encoding leptin can be randomly made in a manner so as not to result in more than 10% variation in the encoded protein. Alternatively, random muteins can be tested for stringent hybridization to the DNA of leptin. Those variants, or the hybridizing DNA, can then be cloned so as to produce an expression product of the DNA in question, and that expression product tested by the simple cell proliferation assay to determine if it inhibits the IGF-I-induced or insulin-induced proliferation of the human breast cancer cell line T-47D or MCF7. Any such variants that have these properties fall within the scope of the claim. Anything else does not. These steps do not involve undue experimentation.

The amount of experimentation that may be permitted in order to satisfy the enablement requirement of 35 U.S.C. §112 is discussed in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In this regard, *Wands* states, 858 F.2d at 736-737, 8 USPQ2d at 1404:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "The key word is 'undue,' not 'experimentation.'"
>
> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard

> for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878-879; 169 USPQ 759, 762-763 (2d Cir. 1971), *cert. denied,* 404 U.S. 1018, 30 L. Ed. 2d 666, 92 S. Ct 680 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed***. [Footnotes omitted - the latter quote being from *In re Jackson,* 217 USPQ 804, 807 (Bd. App. 1982)]

Wands goes on to state, 858 F.2d at 737, 8 USPQ2d at 1404:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [Footnotes omitted]

In analyzing these factors in this case, the conclusion must be reached that the experimentation is not undue. As to the first factor, the quantity of experimentation may be significant, as mutations would have to be generated and screening conducted. However, in the *Wands*

case, it was found that routine screening does not necessarily amount to undue experimentation.

With respect to the second factor, the amount of guidance or direction presented, the specification states, at page 8, line 23-24:

> These muteins are prepared by known synthesis and/or by site-directed mutagenesis techniques, or any other known techniques suitable therefor.

Less guidance is needed for such well-known techniques. Substantial guidance as to a specific screen is provided in Examples 1-9 at pages 16-19 of the present specification.

As to the third factor, the presence or absence of working examples, the assays in examples 1-9 are sufficiently detailed to serve as working examples.

As to the fourth factor, the nature of the invention, the nature of the invention is such that substantial experimentation is acceptable. As will be discussed in the following factors, the field of this invention requires a very high level of skill in the art, and practitioners are well inured to screening that takes substantial experimentation quantitatively.

As to the fifth factor, the state of the prior art, synthesis and site-directed mutagenesis techniques, as well as stringent hybridization techniques, and cell proliferation assays, are all well-documented in the prior art. The

examiner has not doubted this fact, and so it has not been necessary to submit evidence proving it. The present invention does not involve any of these specific techniques *per se*. Their use on the sequence used in the method of the present invention is the advance made by the present inventors.

As to the sixth factor, the relative skill of those in the art, those of ordinary skill in the art of recombinant DNA technology is very high, usually requiring a Ph.D. and/or substantial laboratory experience. For such persons, a greater amount of experimentation would be considered to be routine than for technologies requiring a lower level of skill in the art.

As to the seventh factor, the predictability of the art, predictability is not relevant here, as no predictability is necessary. One need only do the experiments and screen; the results will provide all of the answers. It is not necessary to predict the answers in advance.

As to the eighth factor, the breadth of the claims, paragraph (b) of claim 28 is not so broad so as to require undue experimentation to find what would fall within it for the reasons as discussed above with respect to all of the other factors.

Accordingly, as in *In re Wands*, analysis of the facts of the present case, considering the factors enumerated in *Ex parte Forman*, leads to the conclusion that undue experimentation would not be required to practice the invention. There was a high level of skill in the art at the time when the application was filed and all of the methods needed to practice the invention were well known. Accordingly, reconsideration and withdrawal of this rejection is respectfully urged.

Claims 2, 3, 6, 7, 28 and 29 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Tanaka in view of Cohen. The examiner states that Tanaka teaches that the insulin receptor substrate is upregulated in hepatocellular tumors at both the protein and the RNA level, and that hIRS-1 overexpression promotes neoplastic transformation of NIH3T3 cells and clones transfected with hIRS-1 exhibit the phenotypic properties of transformations. The examiner states that Tanaka teaches that hIRS-1 overexpression induces cellular transformation in an IGF-I-dependent manner, and that IRS-I signaling pathways may be involved as the general mechanism of cellular transformation in the liver. The examiner states that Tanaka teaches that IRS-1 is a major intracellular substrate of IGF-I, and insulin receptors, and such receptors directly interact with the

phosphotyrosine binding domain of IRS-1, and that IGF-I signals have been found necessary to promote tumorgenicity *in vivo* and that the cellular transformation pathway may be specifically mediated through IRS-1. The examiner states that Cohen teaches that leptin downregulates the insulin-dependent tyrosine phosphorylation of IRS-1 in HepG2 cells, which is a human hepatocellular carcinoma cell line, and that the most profound effect of leptin was a reduction in the amount of a tyrosine-phosphorylated 185 kD protein, identified as the insulin receptor substrate. The examiner states that it would have been *prima facie* obvious to administer leptin in order to reduce tyrosine phosphorylation of IRS-1 in patients having hepatocellular carcinoma. The examiner considers that there would have been a reasonable expectation of success in view of the teachings of Tanaka on the correlation between IGF-1 signaling through the phosphotyrosine binding domain of IRS-1, and the promotion of tumorigenesis *in vivo* mediated by hIRS-1, and the teachings of Cohen et al on the profound reduction in the amount of tyrosine-phosphorylated IRS-1 in hepatocellular carcinoma cells treated with leptin. Thus, the examiner considers that one of ordinary skill in the art would have been motivated to administer the leptin to block the tyrosine phosphorylation of IRS-1, and subsequently decrease the

signaling cascade of the insulin and IGF-1 receptors. This rejection is respectfully traversed.

The examiner has not established a *prima facie* case of obviousness in view of the fact that a person of ordinary skill in the art carefully reading these two references would not have had a reasonable expectation that leptin would be effective for treating tumors in mammals or for inhibiting tumor cell proliferation in mammals. Tanaka shows that phosphorylation of tyrosine residues at positions 897 and 1180 within the IRS-1 protein is required for its transforming activity. Cohen showed that leptin reduces tyrosine phosphorylation of IRS-1. However, IRS-1 has at least eight tyrosine residues, and Cohen did not specify which of these residues would be effected by leptin. Accordingly, it would not have been obvious that leptin would specifically inhibit the phosphorylation of residues 897 and 1180, and hence inhibit the transforming activity of phosphorylated IRS-1. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 2, 3, 6, 7, 28, 29, 34 and 35 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Tanaka and Cohen, and further in view of Carter. The examiner states that claim 34 is drawn to the method of claim 28, wherein the active agent is a fusion protein comprising

leptin, and claim 35 embodies the method of claim 34, wherein the active agent is a leptin fusion protein. The examiner states that the combination of Tanaka and Cohen have been discussed in the previous rejection, and that Carter teaches a fusion protein comprising leptin. Thus, the examiner considers it to have been *prima facie* obvious to substitute the leptin immunoadhesin for leptin in the method rendered obvious by the combination of Tanaka and Cohen. This rejection is respectfully traversed.

The combination of Tanaka and Cohen does not make obvious the use of leptin for the treatment of tumors for the reasons discussed above. Carter adds nothing to the deficiencies of Tanaka and Cohen in this regard. Accordingly, this rejection must fall for the same reasons as discussed above with respect to the previous rejection. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

New claim 40 has now been added, which is specifically directed to a method for treatment of human breast carcinoma. The mutein of paragraph (b) requires 90% identity, and does not include the hybridization language. Claim 41 is dependent from claim 40 and excludes muteins from the definition of the active agent. Claim 41 would not be subject to any of the rejections of record, and thus should be

indicated to be in condition for allowance. It is further urged that claim 40 is in condition for allowance, as the enablement rejection should be withdrawn for a claim requiring at least 90% identity, for the reasons discussed above.

It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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